MAJOR ARTICLE

Nationwide Surveillance of Nasopharyngeal *Streptococcus pneumoniae* Isolates from Children with Respiratory Infection, Switzerland, 1998–1999

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The surveillance of pneumococcal antibiotic resistance and serotype distribution is hampered by the relatively low numbers of invasive pneumococcal infections. In Switzerland, a nationwide sentinel surveillance network was used to assess antibiotic resistance and serotype distribution among 1179 pneumococcal isolates cultured from 2769 nasopharyngeal swabs obtained from outpatients with acute otitis media or pneumonia during 1998 and 1999. The proportion of penicillin-susceptible pneumococcal isolates overall (87%) and among infants <2 years old (81%) was comparable to that of invasive isolates (90% and 81%, respectively). The high number of nasopharyngeal isolates allowed for the detection of a rapid increase in the number of penicillin-nonsusceptible pneumococcal (PNSP) strains in the West region of Switzerland, partly because of an epidemic caused by the 19F clone of *Streptococcus pneumoniae*. Clustering of risk factors for the carriage of PNSP isolates further explained the geographic variation in resistance rates. The nationwide sentinel surveillance of nasopharyngeal pneumococcus proved to be valuable for the monitoring of antibiotic resistance, risk factors for carriage of PNSP isolates, and serotype distribution and for the detection of the emergence of a new epidemic clone.

Streptococcus pneumoniae remains one of the most important human pathogens that causes severe invasive infections (e.g., meningitis, sepsis, and pneumonia) and frequent upper respiratory tract infections (e.g., acute otitis media [AOM]). Of additional concern is the increasing frequency and rapid spread of drug-resistant pneumococcal strains worldwide. Surveillance of antibiotic resistance prevalence and identification of risk factors for the emergence and spread of resistant strains at local, national, and international levels are primary strategies in combating antibiotic resistance [1–3]. In addition, the introduction of the new conjugated pneumococcal polysaccharide vaccines stresses the need for intensified surveillance of *S. pneumoniae* for timely recognition of serotype redistribution and the emergence of new serotypes [4, 5].

Surveillance of *S. pneumoniae* is demanding. It must include invasive and noninvasive pneumococcal infections, antibiotic resistance prevalence, and capsular serotype distribution, as well as relevant sociodemo

Received 14 August 2002; revised 24 October 2002; electronically published 29 January 2003.

Presented in part: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 26–29 September 1999 (abstract 1042); 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, 16–20 September 2000 (abstract 18093).

This study was performed according to the guidelines on conduct of clinical research of the ethical committee of the State of Bern. Informed consent was obtained from the children's parents by physicians in the Sentinel Working Group.

Financial support: Swiss National Science Foundation (grant 3100-052955.97/1 to K.M.); Bayer; Bristol Mayers; GlaxoSmithKline; Grünenthal; Lilly; Pfizer.

No author has a commercial or other association that might pose a conflict of interest.

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The Journal of Infectious Diseases 2003; 187:589–96

0022-1899/2003/18704-0008$15.00

graphic and clinical data. However, pneumococcal epidemiology poses several challenges to valid and comprehensive surveillance. First, documented invasive pneumococcal infections are relatively rare, which leads to statistical problems, especially after risk-group analysis. Second, some *S. pneumoniae* serotypes exhibit a distinctive epidemiology, with regard to their potential to cause invasive disease, their predominance in certain age groups, and their geographic distribution. Adequate sample sizes are required for data stratification and detection of such disease-specific serogroup differences [6]. Third, the observed frequency of invasive infections and serotype distribution may be biased by the practice of taking blood cultures [7]. Fourth, valid diagnostic tests for the identification of noninvasive pneumococcal infections are not available, such as tests for pneumonia, or are not routinely used, such as tests for tympanocentesis. Finally, serotyping is not performed routinely in most clinical microbiology laboratories, which requires setting up a reference laboratory. In 1996, the Centers for Disease Control and Prevention (CDC) recommended that nasopharyngeal isolates be used for the surveillance of the pneumococcal epidemiology, since they can be obtained in higher numbers than invasive isolates [1].

In addition, epidemiological data on nasopharyngeal pneumococci harbor valuable information. At the population level, the prevalence of antibiotic resistance among nasopharyngeal pneumococci has been found to be a valid estimate for the strains involved in AOM [8]. In patients with AOM, a culture result from a nasopharyngeal swab that is negative for pneumococcus has a high negative predictive value (i.e., the likelihood of *S. pneumoniae* being present in the middle-ear fluid is very low [9]). In addition, if pneumococcus can be cultured from such a swab but shows no antibiotic resistance traits, the likelihood of a resistant pneumococcus in the middle-ear fluid is small [9].

In the present study, an established nationwide sentinel surveillance network was used to evaluate the antibiotic resistance prevalence and serotype distribution in nasopharyngeal samples from outpatients with AOM or pneumonia in Switzerland during 1998 and 1999. The Swiss Federal Office of Health (SFOH) simultaneously conducted another nationwide surveillance study on invasive pneumococcal infections [10], which allowed for the comparison of the results obtained from nasopharyngeal and invasive isolates.

METHODS

Swiss Sentinel Surveillance Network. The Swiss Sentinel Surveillance Network was established in 1986 (http://www.admin.ch/bag/sentinella/). It consists of a selected sample of practitioners who represent the country geographically and demographically. The total number of participants per subspecialty in the network is defined as a percentage of all Swiss practitioners in the corresponding specialty (i.e., ~3% of general practitioners, 10% of pediatricians, etc.), according to the statistics of the Swiss Medical Association (available at http://www.fmh.ch/). For the selection process, the country is divided into a grid of 240 cells, considering the distribution of all physicians (by subspecialty), the 26 political states (cantons), and urban versus rural regions. The number of participating physicians in each cell is then determined as a proportion of all physicians in that cell. Recruitment of participants is done by annual open advertisement and direct contact through regional representatives. Participation is voluntary. A recent analysis showed that participating physicians are representative of the whole collective of Swiss practitioners [11]. In 1999, the nationwide network comprised 231 regularly reporting participants (130 general practitioners, 66 internists, and 35 pediatricians), accounting for ~3.5% of Swiss practitioners. Anonymous, patient-related data for an average of 5 projects/year, such as influenza, measles, mumps, rubella, pertussis, and asthma, are reported to the SFOH on a weekly basis.

Collection of isolates and data. Between 1 January 1998 and 31 December 1999, participating practitioners submitted nasopharyngeal swabs of outpatients <17 years old or >64 years old who presented with AOM or pneumonia, according to CDC definitions (available at http://www.cdc.gov/epo/dphsi/casedef/index.htm). Only results for the pediatric population <17 years old are presented here. Swabs were obtained with twisted wire rayon tipped applicators (Copan Ventury Transystem; Copan). All samples were sent to the Institute for Infectious Diseases (University of Bern) for microbiological analysis. Patients were enrolled repeatedly for each new episode of AOM or pneumonia. With each sample, practitioners submitted a standardized questionnaire listing the patient's age, sex, place of residence, diagnosis, antibiotic treatment during the previous 8 weeks (yes or no), the number of AOM episodes during the last 12 months, and current day care attendance (yes or no).

Microbiological methods. Swabs were plated onto Columbia agar with 5% sheep blood and incubated at 35°C in a 5% CO_2-enriched atmosphere for 48 h. *S. pneumoniae* was identified by colony morphology and inhibition with optochin. One morphotype per plate was subcultured and frozen at −80°C (Protect; Technical Service).

All isolates were tested against oxacillin (1 μg disc), erythromycin, and cotrimoxazol by the disc diffusion method [12]. For isolates with reduced susceptibility against any of these 3 antibiotics, MICs were determined against penicillin, erythromycin, cotrimoxazol, azithromycin, cefaclor, cefprozil, ceftriaxon, cefuroxime, chloramphenicol, ofloxacin, tetracyclin, and vancomycin, by use of the E-test method (AB Biodisk), according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines [12]. MICs for gatifloxacin and rifampicin were determined using the E-test method for penicillin-nonsusceptible pneumococcal (PNSP) isolates (defined as

Table 1. Characteristics of 1179 pediatric pneumococcal isolates from the Swiss Sentinel Study on pneumococcus, 1998–1999.

Characteristic	PSP	PNSP	*P*
Total	1022 (86.6)	157 (13.4)	
Diagnosis			
AOM	966 (94.5)	145 (92.4)	
Pneumonia	45 (4.4)	11 (7.0)	
Age, years			<.001
0–1	291 (28.5)	69 (43.9)	
2–4	373 (36.5)	48 (30.6)	
5–16	358 (35.0)	40 (25.5)	
Female	515/1022 (50.4)	73/157 (46.5)	
Antibiotic therapy in the last 8 weeks[a]	160/894 (17.8)	40/142 (28.2)	.005
Currently attending day care[a]	135/858 (15.7)	33/142 (23.2)	.03
>1 episode of AOM in the last 12 months[a]	157/857 (18.3)	38/141 (26.9)	.003
West region of Switzerland[a]	549/1016 (54.0)	117/157 (74.5)	<.001
Drug to which isolate is susceptible[b]			
Erythromycin	935 (91.5)	87 (55.4)	<.001
Cotrimoxazol	885 (86.5)	92 (58.5)	<.001
Gatifloxacin	100 (100)	153 (100)	
Rifampicin	100 (100)	153 (100)	
Serotype or serogroup[c]			
4	5 (1.6)	0 (0)	
6B	32 (10.5)	14 (9)	
9V	11 (3.6)	9 (5.8)	
14	30 (9.9)	20 (12.9)	
18C	9 (3.0)	0 (0)	
19F	55 (18.1)	40 (25.8)	.05
23F	34 (11.2)	11 (7.1)	
Total	304 (100)	155 (100)	
Future vaccine types (1, 3, 5, or 7F)	19 (6.3)	2 (1.3)	
6A	27 (8.9)	6 (3.9)	.04
19A	10 (3.3)	13 (8.4)	.01
Other types	72 (23.6)	43 (25.8)	
7-V PnCC[d]	176 (57.9)	94 (59.9)	
9-V PnCC[d]	180 (59.2)	95 (60.5)	
11-V PnCC[d]	195 (64.1)	96 (61.1)	

NOTE. Data are no. (%) of isolates, except where noted. Of the 1179 pneumococcal isolates, 288 (24.4%) were from patients with repeated new episodes of acute otitis media (AOM) or pneumonia; of these, 18% had 2 swabs taken (2 disease episodes). PNSP, penicillin-nonsusceptible pneumococci; PSP, penicillin-susceptible pneumococci.

[a] Data are no./total no. (%) of isolates. Logistic regression analysis for risk factors of carriage of PNSP isolates yielded the following crude odds ratios (cORs), adjusted odds ratios (aORs), and 95% confidence intervals (CIs). Age: 0–1 years old, reference; 2–4 years old, cOR = 0.54 and aOR = 0.56 (95% CI, 0.37–0.85); and 5–16 years old, cOR = 0.47 and aOR = 0.45 (95% CI 0.29–0.71); antibiotic therapy: cOR = 1.79 and aOR = 1.65 (95% CI, 1.10–2.45); >1 episode of AOM: cOR = 1.64 (95% CI, 1.09–2.48); currently attending day care: cOR = 1.62 (95% CI, 1.05–2.49); West region of Switzerland: cOR = 2.48 (95% CI, 1.70–3.64). Only age and antibiotic therapy remained independent risk factors after adjustment and were included in the final model.

[b] Susceptibilities to gatifloxacin and rifampicin were tested in a random sample of 100 PSP isolates and in 153 of a total of 157 PNSP isolates.

[c] Serogroup or serotype was determined for 155 of 157 PNSP isolates.

[d] 7-V PnCC, expected coverage for the conjugated 7-valent (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) pneumococcal vaccine; 9-V PnCC, expected coverage for the 9-valent (7-V PnCC plus serotypes 1 and 5) pneumococcal vaccine; and 11-V PnCC, expected coverage for the 11-valent (9-V PnCC plus serotypes 3 and 7F) pneumococcal vaccine.

Table 2. Geographic distribution of pneumococcal susceptibility and risk factors for carriage of penicillin-nonsusceptible pneumococcal isolates among children with respiratory infections, Swiss Sentinel Study, 1998–1999.

Drug, year, age group	West[a]	East[a]	OR (95% CI)	*P*
Penicillin				
1998				
<2 years	93 (80.2)	48 (88.9)		.2
<17 years	317 (85.2)	220 (91.6)		.01
1999				
<2 years	78 (70.9)	71 (89.9)		.003
<17 years	232 (78.9)	247 (92.5)		<.001
Erythromycin				
1998				
<2 years	96 (82.8)	49 (90.7)		.15
<17 years	316 (84.9)	215 (89.5)		.09
1999				
<2 years	84 (76.4)	70 (88.6)		.02
<17 years	239 (81.3)	248 (92.8)		<.001
Cotrimoxazol				
1998				
<2 years	92 (79.3)	46 (85.2)		.48
<17 years	303 (81.4)	209 (87.1)		.06
1999				
<2 years	68 (61.8)	64 (81.0)		.007
<17 years	208 (70.7)	224 (83.9)		<.001
Demographic characteristics[b]				
Antibiotic therapy in previous 8 weeks	139/571 (24.3)	60/459 (13.1)	2.00 (1.40–2.77)	<.001
>1 episode of AOM in the last 12 months	146/554 (26.4)	49/438 (11.9)	2.71 (1.90–3.87)	<.001
Currently attending day care	113/547 (20.7)	53/447 (11.9)	1.96 (1.36–2.85)	<.001

NOTE. Data are no. (%) of isolates, except where noted. AOM, acute otitis media; CI, confidence interval; OR, odds ratio (adjusted for age and study year [1998 or 1999]).

[a] Information on place of residency was missing for 6 patients.

[b] Data are no./total (%) of isolates.

MIC >0.06 mg/L) and a random sample of 100 penicillin-susceptible pneumococcal (PSP) isolates. Interpretation of MICs was done according to NCCLS guidelines, with the exception of gatifloxacin (sensitive, ⩽1 mg/L; resistant, ⩾4 mg/L) [13].

Capsular typing was done on all isolates with reduced susceptibility to penicillin, erythromycin, or cotrimoxazol (n = 364). In addition, a random sample of 95 PSP isolates was chosen for serotyping using a random number table. The Quellung reaction was performed using antiserum from the Statens Serum Institute (Copenhagen).

Pulsed-field gel electrophoresis (PFGE) typing was done on all isolates of serogroup 19, as described elsewhere [14], by use of *Sma*I for restriction of chromosomal DNA. Isolates were grouped into the same clone if they shared the same capsule type and if their pattern differed by ⩽3 bands [15]. Representative strains of 19F clones were further analyzed by multilocus sequence typing (MLST), as described elsewhere [16].

Statistical analysis. Risk factors for pneumococcal carriage with PNSP isolates were evaluated by univariate and multivariate analysis. Variables were coded as described above. Two geographic regions were defined: the East region, which represents largely the German-speaking part of Switzerland, together with the much smaller Italian- and Roman-speaking regions, and the West region, which represents largely the French-speaking cantons. It is well known that the Swiss German and the French population differ according to several sociodemographic and socioeconomic factors, including behaviors and political orientation.

Risk factors identified by univariate statistics were entered into a logistic regression model using StatView (version 5.0; SAS Institute). The final model contained the largest number of variables, with $P \leqslant .05$. Proportions were compared with the

χ^2 or Fisher's exact test, as appropriate. Differences between means were assessed by the Student's *t* test. A cutoff of 2-tailed $P \leq .05$ was used for all statistical analyses.

RESULTS

Samples analyzed. In total, 2769 nasopharyngeal swabs were cultured from children <17 years old, and *S. pneumoniae* was isolated from 1179 (43%) of these samples. The age-specific carriage rates were as follows: 48.3% for the 0–1-year-old group, 48.1% for the 2–4-year-old group, and 38.7% for the 5–16-year-old group. These carriage rates compared well with those found in other studies [17, 18]. Of the 1179 pneumococcal isolates, 288 (24%) were from patients who had repeated swabs taken; 210 (73%) patients had 2 swabs taken. Isolates from the same patients were sampled at least 2 months apart. The isolates were evenly distributed between the study years and the 2 defined geographic regions (data not shown). Study patients predominantly had AOM (93%). Nineteen percent of study patients had received antibiotics during the preceding 8 weeks, ~20% had >1 episode of AOM during the last 12 months, and ~17% were attending day care at the time of the outpatient visit.

Antibiotic susceptibility rates. Overall susceptibility of pneumococcal isolates was 87% for penicillin, 87% for erythromycin, and 81% for cotrimoxazol. High resistance to penicillin (MIC >1 mg/L) was rare (29/1179 isolates [2.5%]), and the highest observed MIC against penicillin was 12 mg/L. MICs for erythromycin showed a bimodal distribution (data not shown); most PNSP isolates (111/142 [78.1%]) had MICs >32 mg/L, which is compatible with a macrolide, lincosamide, and streptogramin B resistance phenotype [19]. Multidrug resistance was frequent among PNSP isolates (table 1). Half the PNSP isolates were resistant to macrolides and cotrimoxazol. Susceptibility rates among PNSP isolates to other antibiotics were as follows: cefaclor, 45.7%; cefprozile, 73.2%; cefuroxime, 75.1%; ceftriaxone, 84.3% (no high level resistance); chloramphenicol, 85.6%; ofloxacin, 71.0%; tetracyline, 51.0%; and vancomycin, 100%. The proportion of PNSP isolates and cotrimoxazol-resistant strains increased rapidly between 1998 and 1999, primarily in the youngest age group residing in the West region of Switzerland; in 1999, it reached 29% for penicillin and 38% for cotrimoxazol (table 2).

Risk factors for carriage of PNSP isolates. Carriage of PNSP isolates was significantly associated with age <2 years, antibiotic therapy during the last 8 weeks, >1 episode of AOM during the past 12 months, and current day care attendance (table 1). In the logistic regression model, only age and recent antibiotic therapy remained independent risk factors (table 1). Resistance rates also were considerably higher in the West region of Switzerland, especially among children <2 years old (table 1). This result could be explained by a significantly higher prevalence of the risk factors for carriage of PNSP isolates in the West region (table 2). Children residing in the West region were twice as likely to have received antibiotic therapy, had a 2–3-fold higher probability of recurrent AOM, and were 20% more likely to attend day care than children in the East region.

Table 3. Serotype distribution among 304 penicillin-susceptible pneumococcal (PSP) and 155 penicillin-nonsusceptible pneumococcal (PNSP) nasopharyngeal isolates, by geographic region and age, Swiss Sentinel Study, 1998–1999.

Serotype	Region		Age <2 years	
	East	West	PSP	PNSP
1	1 (0.6)	4 (1.4)	0 (0)	0 (0)
3	9 (5.3)	6 (2.1)	4 (4.1)	0 (0)
4	4 (2.4)	1 (0.3)	4 (4.1)	0 (0)
5	0 (0)	0 (0)	0 (0)	0 (0)
6B[a]	11 (6.5)	35 (12.1)	12 (12.4)	7 (10.1)
7F	1 (0.6)	0 (0)	0 (0)	0 (0)
9V	9 (5.3)	11 (3.8)	3 (3.1)	5 (7.2)
14	18 (10.7)	32 (11)	12 (12.4)	6 (8.7)
18C	6 (3.6)	3 (1)	3 (3.1)	0 (0)
19F[a]	27 (16.0)	68 (23.4)	22 (22.7)	21 (30.4)
19F clone[a]	8 (4.7)	38 (13.1)	7 (7.2)	8 (11.6)
23F[a]	7 (4.1)	38 (13.1)	12 (12.4)	6 (8.7)
7-V PnC[b]	82 (48.5)	188 (64.8)	68 (70.1)	45 (65.2)
9-V PnC[b]	83 (49.1)	192 (66.2)	68 (70.1)	45 (65.2)
11-V PnC[b]	93 (55.0)	198 (68.3)	72 (74.2)	45 (65.2)
6A	0 (0)	1 (0.3)	4 (4.1)	4 (5.8)
19A	6 (3.6)	17 (5.9)	3 (3.1)	8 (11.6)
Other	70 (41.4)	74 (25.5)	18 (18.5)	12 (17.3)
Total	169 (100)	290 (100)	97 (100)	69 (100)

NOTE. Data are no. (%) of isolates.

[a] Serotypes 6B ($P = .05$), 19F ($P = .05$), 19F clone ($P = .006$), and 23F ($P = .003$) occurred significantly more frequently in the West region. "19F clone" refers to the most frequent serotype 19F clone observed in this study.

[b] Expected coverage for the conjugated 7-valent (7-V PnC: serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) pneumococcal vaccine, the conjugated 9-valent vaccine (7-valent plus serotypes 1 and 5), and the conjugated 11-valent vaccine (9-valent plus serotypes 3 and 7F).

Serogroup distribution. Serogroup 19 and serotype 19F were the most frequent serogroups observed (table 1). Serotypes 19F and 19A were significantly associated with PNSP isolates (table 1) and residence in the West region (table 3). In addition, serogroup 19 occurred most frequently among children <2 years old (table 3). Besides serotype 19F, the most prevalent serotypes among PSP and PNSP isolates were, in decreasing order of frequency, 23F, 6B, and 14 (table 3). None of these other serotypes showed a similar association with PNSP. However, serotypes 6B and 23F also were more prevalent in the West than in the East region (table 3). The expected coverage for the new 7-valent conjugated pneumococcal vaccine was, on

average, 60% (table 1). However, the expected coverage is ~70% for children <2 years old and would be considerably higher in the West than in the East region (table 3).

Molecular typing of 19F strains. PFGE revealed 4 clones of serotype 19F of 46, 14, 4, and 2 isolates and 29 sporadic strains. The largest clone comprised 21 PSP and 25 PNSP isolates. MIC_{50} and MIC_{90} values to penicillin for PNSP isolates were relatively low (0.094 mg/L). MLST revealed the following allelic combination: aroE type 7, gdh type 14, gki type 4, spi type 1, recP type 12, xpt type 1, and ddl type 14. According to the MLST database (available at http://www.mlst.net/), this clone did not correspond to any of the known, multidrug-resistant clones [20]. Overall carriage of serotype 19F and carriage of the most frequently observed 19F clone were not more associated with prior antibiotic therapy, recurrent AOM, and day care attendance than other serotypes observed in this surveillance study (data not shown).

Epidemic spread of serotype 19F clone. The relative proportions of serotype 19F isolates increased between 1998 and 1999 from 10.8% (13/120) to 22.8% (42/184) among PSP isolates ($P = .01$, χ^2 test) and from 20.5% (15/73) to 30.5% (25/82) among PNSP isolates ($P = .10$, χ^2 test). This change was largely due to the spread of the largest 19F clone described above. After subtracting the number of isolates belonging to the most frequent serotype 19F clone from the total number of 19F isolates, the proportions of 19F strains in 1998 (8.8%) and 1999 (12.0%) were not significantly different. Carriage of the serotype 19F clone was associated with residence in the West region (table 3). In addition, the rapid increase in PNSP isolates in the West region in 1999 was due, at least in part, to this clone. Of interest, PSP isolates of this serotype 19F clone increased first in the West region and then spread to the East region; the increase of PNSP isolates among this 19F clone was, however, almost limited to the West region (figure 1).

DISCUSSION

The present study made use of an established sentinel network of practitioners to assess the value of randomly collected nasopharyngeal swabs for nationwide pneumococcal surveillance. A concurrent, nationwide, laboratory-based study of invasive *S. pneumoniae* isolates allowed us to compare the 2 different surveillance strategies [10].

In January 1998, invasive *S. pneumoniae* infections (defined as the culture of pneumococcus from a sterile body site) became a reportable disease in Switzerland. At the same time, a 2-year pilot study was started on the collection of invasive *S. pneumoniae* isolates from clinical microbiology laboratories in a reference laboratory. Over a period of 18 months (April 1998 to September 1999), 925 isolates were received by the reference

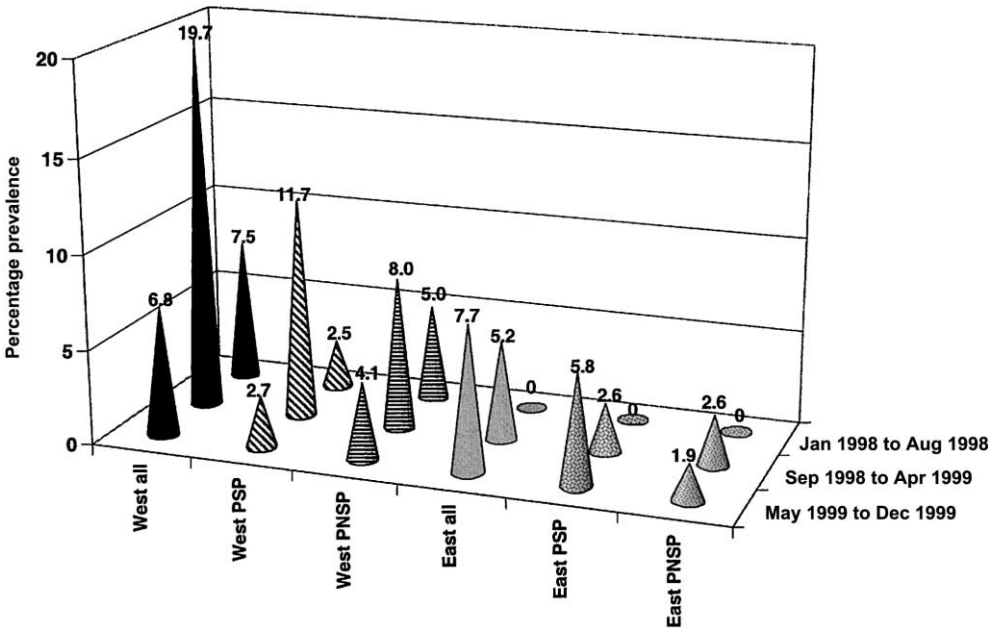

Figure 1. Differential dynamics of spread of the most prevalent observed serotype 19F clone between 1998 and 1999 in the East and West regions of Switzerland. The surveillance period was stratified into 3 different time intervals, as indicated on the *Z*-axis. The percentage prevalence of serotype 19F clone is given regardless of susceptibility to penicillin ("West all" and "East all"), for penicillin-susceptible pneumococcal (PSP) isolates, and for penicillin-nonsusceptible pneumococcal (PNSP) isolates. There were 6 serotype 19F clone isolates in January 1998 to August 1998 , 31 serotype 19F clone isolates in September 1998 to April 1999, and 9 serotype 19F clone isolates in May 1999 to December 1999. The difference between East and West for the proportions of all serotype 19F clone isolates was statistically significant for the time intervals September 1998 to April 1999 ($P = .001$, χ^2 test) and May 1999 to December 1999 ($P = .04$, χ^2 test).

center from 61 laboratories (of 77 contacted laboratories) and were tested for antibiotic susceptibility and capsular serotype [10]. The proportion of isolates from children <17 years old was 14.9% (138 isolates).

Overall penicillin susceptibility rates for children <17 years old were similar for nasopharyngeal (87%) and invasive isolates (90%) [10]. In addition, children <2 years old had the lowest susceptibility rates, with 81% in both studies. However, only the ~6-fold higher number of isolates obtained in the Sentinel Study for children <2 years old (359 vs. 63 isolates) allowed for a detailed analysis of resistance data. For example, only the Sentinel data revealed the rapid increase of resistance rates between 1998 and 1999 in infants residing in the West region of Switzerland. Resistance rates in nasopharyngeal and invasive strains did not agree as well in a recent Canadian study as in the data presented here; however, in the Canadian study, isolates from children attending day care were compared with invasive strains from the whole population, which may account for the slightly higher resistance rates in the former [21].

The serotype distribution was similar between the nasopharyngeal and invasive pneumococcal isolates with regard to the most prevalent types, but the exact rank order differed. This was equally the case for the overall serotype distribution among children <17 years old and the distribution of serotypes among the age group <2 years old. Serotype 19F was the most prevalent type in nasopharyngeal isolates, whereas serotypes 14 and 1 predominated among invasive strains. The relatively high proportion of serotype 19F in the Sentinel study is likely to be the result of the epidemic spread of a new serotype 19F clone not yet seen in the invasive isolates. It may be that the rapid epidemic spread of a serotype clone is reflected in invasive isolates only after a certain lag time and that nasopharyngeal isolates are a more-sensitive indicator for emerging clones. The relative predominance of serotype 1 among invasive strains is characteristic of European countries [22].

This Sentinel study also allowed us to identify previously described risk factors for carriage of PNSP isolates (i.e., young age, recurrent AOM, previous antibiotic treatment, and day care attendance) [17, 23, 24]. The ~2-fold higher prevalence of some of the identified risk factors for PNSP isolate carriage in the West region of Switzerland is likely to play an important role for the higher resistance prevalence observed in this region. No data on the specific antibiotics prescribed were obtained in this study. Therefore, there are no data to explain the rapidly increasing resistance to cotrimoxazole in the West region; however, use of this drug for prophylaxis against recurrent AOM is a common practice in the West region of Switzerland.

The Sentinel Surveillance Network detected a new epidemic serotype 19F clone. By use of MLST, this clone was not identical or closely related to any of the described major multidrug-resistant clones of *S. pneumoniae* [20]. According to the MLST database, 2 strains have been recorded so far, both in Spanish patients with meningitis in 1997. Recently, this clone also was observed among clones isolated in day care centers in Portugal [25]. The reason for the rapid epidemic spread of this 19F clone in Switzerland remains unexplained. It is intriguing that the clone comprises PSP and PNSP isolates and that only PSP strains spread to the East region. We are currently analyzing the characteristics of this clone and the question of whether PNSP strains arise constantly de novo from PSP strains or are predominantly transmitted.

Surveillance of nasopharyngeal isolates allows for the analysis of large numbers of isolates, which is an advantage over invasive isolates. However, even with the sentinel approach, the number of available nasopharyngeal isolates in a nationwide surveillance may be unnecessarily high for statistical precision and too abundant for logistical reasons. The present study was, therefore, restricted to children. This action was also motivated by the fact that this patient group may have the greatest immediate benefit from the obtained results at both the individual and population levels for the choice of empiric therapy for AOM and pneumonia [8, 9]. Whether the observed data also can be extrapolated to children without AOM or pneumonia and the age groups not covered by this study would have to be investigated by use of other sampling algorithms. However, a recent study did not find vast differences for resistance rates and serotype distributions between nasopharyngeal pneumococci isolated from healthy infants and infants with respiratory disease [18].

Therefore, nationwide sentinel surveillance of nasopharyngeal pneumococcus provided valuable data on antibiotic resistance prevalence, risk factors for carriage of PNSP strains, and serotype distribution. It allowed us to detect the epidemic emergence of a new 19F clone associated with the spread of antibiotic resistance. These features will be of importance for pneumococcal surveillance in the era of the new conjugate polysaccharide vaccines. In particular, they will allow for documentation of serotype replacement after the introduction of widespread vaccination.

Acknowledgments

We thank Suzanne Aebi for excellent technical assistance and Sara Droz for organizational support.

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